THE SECONDARY OLFACTORY AREAS IN THE HUMAN BRAIN

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Neurologists have accepted for many years that olfactory sensation in the human subject are referred ultimately to the uncus, the anterior perforated substance, the septal areas in the subcallosal gyrus and possibly the hippocampal formation. This conclusion is based on the study of normal material, the comparison with Marchi experiments on lower animals and records of cases with lesions which had affected olfaction to a greater or lesser extent. None of these methods alone is entirely reliable, and hitherto it has not been possible to localize at all precisely the olfactory areas in the human brain.

During the past decade the mammalian olfactory connexions have been carefully studied by experimental methods. The observations which have been made unite to show that the distribution of fibres from the olfactory bulb is essentially similar in widely different groups of mammals, despite the marked displacement of the base of the telencephalon which is associated with the expansion of the cerebral cortex (Allison, 1953a). The main secondary olfactory areas have a characteristic arrangement of nerve cell-bodies and fibres. Hence they can usually be distinguished from the adjacent areas, and a satisfactory localization of the olfactory brain can be made on the basis of a study of normal material examined in the light of experimental findings.

This communication represents an attempt to apply the results of animal experimentation to the human brain. The areas in the human brain most probably receiving fibre accessions from the olfactory bulb, which may therefore be designated secondary olfactory areas, are described. The conclusions are based mainly upon a detailed comparison of the human forebrain with that of the monkey (*Macaca* and *Papio*) in which the olfactory connexions have been determined experimentally (Meyer & Allison, 1949). The pathological changes in a human brain following surgical transection of the olfactory tracts on one side provide confirmatory evidence for the conclusions given below.

The voluminous literature covering the morphology of this part of the human brain will not be reviewed here. References to earlier writers will be found in the works of Campbell (1905), Brodmann (1909), Cajal (1911), Johnston (1923), Rose (1927a, b. 1928, 1935), v. Economo (1927), Beck (1934) and Crosby & Humphrey (1941), whose descriptions form the basis of the present analysis.

MATERIAL

Series of 20μ transverse celloidin sections through two normal human brains were available, every twelfth section mounted and stained alternately for cell masses and myelinated fibres.

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The brain of a man aged 52, whose olfactory peduncle had been accidentally severed on one side 2 years before death during a prefontal leucotomy, was made available for examination through the courtesy of Prof. Alfred Meyer of the Institute of Psychiatry, London. The brain had been fixed in formal-saline; every twenty-fifth section of a series of 20μ celloidin sections was mounted and stained with cresyl violet.

One normal human brain (man aged 49, dying of coronary thrombosis) was dissected and photographed; sections 15–20μ thick were cut in a transverse plane and stained by the Nissl, Weil and Bielschowski silver methods. From observations of these sections the position of the olfactory areas was marked on the photographs showing the surface of the brain (Pl. 1, figs. 1, 2). Photomicrographs of Nissl sections included in Pls. 1 and 2 show the disposition of most of the main basal olfactory areas.

OBSERVATIONS

Anterior olfactory nucleus. This nucleus is relatively small in man. In most mammals the nucleus forms a circle around the olfactory ventricle in the olfactory crus, but in man the olfactory crus is much attenuated and the olfactory ventricle obliterated, so that the nucleus is represented only as isolated masses of cells scattered throughout the length of the peduncular fibres. The dorsal part of the nucleus is, as Crosby & Humphrey (1941) state, conspicuous on account of its comparatively large pyramidal cells. The external part of the nucleus appears to be represented by small, discontinuous patches of small, deeply stained neurons, situated at the ventral border of the neocortex and continuing postero-laterally as far as the prepiriform area (it is included in the lateral part of the nucleus of Crosby & Humphrey). The external part of the nucleus had a fascicle of olfactory tract fibres closely associated with it. It is thus probable that in man, as in the monkey and lower mammals, only the dorsal and external parts of the nucleus receive olfactory fibres from the bulb. The other parts of the anterior olfactory nucleus (or area retrobulbaris of Rose) are comparatively small, and their position is described by Crosby & Humphrey.

Olfactory tubercle. The term 'anterior perforated substance' as applied to the human brain often refers to most of the area between the olfactory trigone and the optic chiasma, thus including structures other than the olfactory tubercle in the brains of lower mammals. The term 'olfactory tubercle' is employed here, as Rose and Crosby & Humphrey have used it, to designate the region on the basal surface of the frontal lobe between the olfactory tract (situated antero-laterally) and the nucleus of the diagonal band (which lies postero-medial to it).* This has been sub-divided by both Rose and Crosby & Humphrey, into three areas rostral (tol 1), middle (tol 2) and caudal (tol 3), although perhaps the terms 'antero-lateral', 'middle' and 'postero-medial' might be more appropriate to indicate their relative positions.

The general relationships of the olfactory tubercle in the human brain are the same as those in other mammals. On the surface of the brain the tubercle shows two distinct parts, one, adjacent to the olfactory tract, being smooth and rounded and

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* Many other definitions have been given. Thus Cajal's anterior perforated space includes the diagonal band and the Vogts' (1919) tuberculum olfactorium refers to the olfactory trigone alone (Rose's tol 1 and a small part of tol 2). The present usage is, however, more consistent with that given in the comparative descriptions.

the other perforated by many small blood vessels. In sections the characteristic lamination of the olfactory tubercle is most conspicuous in the antero-lateral part (tol 1 and tol 2): in this region a distinct band of small, closely packed pyramidal cells lies between the superficial plexiform layer and the deep layer of polymorphous cells. Further medially the layers are broken up, islets of Calleja are present (including the large medial islet of small, granular-type cells bordering on the septal areas) and the lamination is either very indistinct or absent altogether (mainly tol 3).

In myelin preparations, and even more clearly in silver preparations, a distinct fascicle of fibres can be traced from the medial side of the olfactory tract to the plexiform layer of the tubercle. These fibres in all probability end for the most part in tol 1, where they are shown on the surface of the brain in Pl. 1, fig. 2. They constitute the small bundle which has been termed 'medial olfactory stria' or 'medial olfacto-frontal fascicle'.

The anterior limb of the anterior commissure system, upon leaving the olfactory peduncle, penetrates the brain substance and comes to lie above the olfactory tubercle along with other small fascicles of fibres. Further posteriorly it joins the antero-ventral side of the relatively enormous mass of fibres belonging to the transverse and temporal limbs of the commissure.

Septal areas. These areas have been shown in the experiments on monkeys to receive very few if any, olfactory fibres directly. This is very probably true of the human brain also: certainly no significant contingent of fibres can be traced from the olfactory tract to the septal region.

Prepiriform cortex. This part of the allocortex has never been properly localized in the human brain. Many authors have described or figured parts of it, but even Cajal, Beck and Rose, who have all studied this region closely, failed to distinguish the olfactory from the non-olfactory cortex.

It has been observed in available material that the prepiriform cortex in the human brain, as in the monkey and lower mammals, has two parts. The frontal part is confined to a small, triangular area on the lateral side of the olfactory tract, and it is partly covered by the expanded neocortex of the medial orbital gyrus (so that in sections taken at some levels the olfactory tract fibres and prepiriform cortex appear to lie not on the surface of the brain but beneath a molecular layer of iso-cortex (Pl. 1, fig. 3). The frontal prepiriform cortex has a typical laminated structure, with a plexiform layer containing fibres from the olfactory tract, a band of fairly deeply stained pyramidal cells, and a polymorphous cell layer with ill-defined internal limits. This area is termed area prepiriformis 2 and 3 by Rose (1927b); part of the agranular insular cortex (parts of *ai* 4 and 5) by Rose (1928) and *Fk* and *Id* by v. Economo (1927).

Continuous at some levels (Pl. 2, fig. 5), with the small area of prepiriform cortex on the orbital surface of the frontal lobe is the much more extensive temporal prepiriform area. The olfactory tract fibres spread over it from the point of termination of the main bundle in the angle between frontal and temporal lobes. These fibres are expended in the plexiform layer, where many are not tangential (as in other cortical areas), but are turned inwards to end in relation to the dendrites of the pyramidal cells. In some regions this cortex presents a typical lamination

(which is very similar to that observed in the monkey or even in the rabbit), but towards the fringe of the area the conspicuous band of pyramidal cells is broken up and small islets of pyramidal cells occur. These are not so large as the very prominent islets in the main part of the entorhinal area, although the boundary between the two types of cortex is not always very distinct. If the disposition of the cells and the extent of the superficial layer of olfactory fibres (which is thicker than the tangential layer of fibres in other cortical areas) are taken together, however, the limits of the prepiriform cortex can be nearly determined (as shown in Pl. 1, fig. 2). Posteriorly, there is a narrow transition area between the prepiriform cortex and the cortical and medial amygdaloid nuclei, as in other animals; anteriorly and laterally the pre-piriform cortex goes over into temporal and insular isocortex.

This primary olfactory cortex has been given various designations. Cajal included in his 'région olfactive centrale' in the human brain part of the entorhinal cortex. Most of the temporal prepiriform area as here defined falls into the entorhinal area of Rose (1927 b)—mainly the anterior part of his $e\gamma$; however, in a later study, Rose (1928) terms the same area agranular insular cortex—parts of ai 9 and ai 10. The temporal prepiriform area is included in v. Economo's area Ha. However, the extent of the temporal prepiriform area does correspond very nearly to that of the area temporalis insulae of Beck (1934), who investigated the myelo-architecture of the dorsal temporal region in detail. Beck ascribed the prepiriform cortex to a very small area on the surface of the temporal lobe immediately adjacent to the olfactory tract; he points out that the main characteristic of the area temporalis insulae is the prominence of the fibrous first layer, which becomes thicker in the posterior part of the area (that is to say, nearest the olfactory tract). Hence it must be concluded that in man, as in the monkey, Beck's area temporalis insulae is the prepiriform area and that the superficial fibrous layer is derived from the olfactory tract.

The temporal prepiriform area thus comprises a considerable part of the cortex of the gyrus ambiens; it is separated by the semi-annular sulcus from the amygdala and by a shallow depression from the main part of the entorhinal area in the hippo-campal gyrus.

Amygdaloid complex. The amygdaloid complex in the human brain has been described by Johnston (1923), Hilpert (1928), Crosby & Humphrey (1941) and others. The terminology of Johnston and of Crosby & Humphrey, which is now standardized, has been employed in this description.

As already stated, most of the olfactory tract fibres turn forward to end in the temporal prepiriform cortex, but a relatively small number of these fibres can be seen passing back to the amygdala, where they apparently terminate in the super-ficial part of the cortico-medial group of nuclei, as in the monkey. Only the cortico-medial group of nuclei will be given consideration here, then; for a fuller account of the large and prominent baso-lateral nuclear masses reference may be made to the text of Crosby & Humphrey.

Nucleus of the lateral olfactory tract. This is represented only by two or three very small masses of deeply stained cells amongst the olfactory fibres between the edge of the medial nucleus and the cortical nucleus. It almost certainly receives olfactory terminals, but it is so much reduced in size that it can hardly be very significant functionally.

Medial nucleus. This nucleus, which lies near the entorhinal fissure, is relatively limited, and consists for the most part of small, rather faintly stained cells. As in the monkey, many olfactory fibres may be seen over the surface of the medial nucleus, and they apparently penetrate quite deeply into its antero-medial part.

Cortical nucleus. This is the largest of the cortico-medial nuclei. Olfactory fibres can be traced into the plexiform layer, where they probably terminate in relation to the dendrites of the neurons in about the anterior third of the nucleus. From analogy with the monkey it is unlikely that the tangential fibres over the more posterior part of the cortical nucleus are olfactory.

Cortico-amygdaloid transition area. The probable homologies of the transition area between the amygdala and the adjacent parts of the piriform cortex have previously been discussed (Meyer & Allison, 1949). It is only necessary to state here that in the human brain two parts of the transition area can be recognized; the smaller anterior part, lying between the prepiriform area and cortical nucleus, appears to receive a considerable accession of olfactory fibres, while the posterior part, which is situated beneath the entorhinal fissure between the cortical nucleus and the entorhinal area, does not in all probability receive any olfactory fibres.

Central nucleus and nucleus of the stria terminalis. The central nucleus is comparatively large and rounded, and it is fairly easily defined in the posterior third of the amygdaloid complex.* Its cells are smaller and stain more lightly than those of the basal complex, which are adjacent to it. The nucleus of the stria terminalis has cells of a similar type; it is small in section and very much attenuated where it lies over the internal capsule, but it expands behind the anterior commissure and extends downwards into the medial preoptic region. The positions of these nuclei are shown in Pls. 1 and 2, figs. 4 and 8. It is not possible, of course, in normal material, to see whether they receive olfactory fibres, but again the analogy with other animals makes it likely that they play some part in olfactory reactions, even though both nuclei are extensive when compared with the relatively small olfactory areas in man.

PATHOLOGICAL MATERIAL

Transection of the olfactory tract in the rabbit is followed after a time interval of about a month by marked trans-synaptic atrophy of the pyramidal cells of the prepiriform area (Winkler, 1918; Allison, 1953b). Uyematsu (1921) described two human brains with unilateral destruction of the olfactory peduncle in which there was cellular atrophy in the piriform cortex. The brain described in the section on material above, in which the olfactory tract had been accidentally severed on the one side by a leucotomy cut 2 years before death, shows similar changes. On the side of the olfactory tract lesion there is a definite shrinkage and pyknosis of the pyramidal cells of the prepiriform area. The cell bodies are so deeply stained that their nuclei are invisible. This atrophic change corresponds precisely to the limits of the prepiriform area as already described on the side of the transection; on the other side, and in the other olfactory areas on both sides, the cellular architecture appears to be normal. The severity of the trans-synaptic atrophy in the cells of the prepiriform cortex presumably reflects the dependence of this part of the brain upon incoming olfactory impulses, while the sparing of the other areas suggests that they may be concerned with other activities as well as olfaction.

* Only the most anterior part of the nucleus is shown in Pl. 2, fig. 8.

COMMENT

The main results of this investigation are indicated in Pl. 1, figs. 1 and 2. They may be summarized briefly by stating that fibres from the olfactory bulb pass through the elongated olfactory crus to join the orbital surface of the frontal lobe. Here the great majority of olfactory tract fibres deviate sharply in a lateral direction (as the lateral olfactory stria) and pass outward to the junction of the frontal and temporal lobes. A thin, superficial band of medullated fibres (the medial olfactory stria) leaves the medial side of the olfactory tract to be expended in the anterior part of the olfactory tubercle; they do not, apparently, reach the septal region of the sub-callosal gyrus. A thin sheet of olfactory fibres spreads out on the lateral side of the tract also; it ends first of all over the small dorsal and external parts of the anterior olfactory nucleus and then over the frontal prepiriform cortex. Most of the olfactory tract fibres, however, reach the temporal lobe, where they are only faintly visible macroscopically because they are spread out as a thin superficial layer over a comparatively wide area. Most of these fibres pass anteriorly or medially to terminate in the plexiform layer of the temporal prepiriform cortex. Others travel in a postero-medial direction from the tract and appear to end in the superficial nuclei of the cortico-medial group in about the anterior one-third of the amygdaloid complex. The olfactory component of the anterior limb of the anterior commissure is a small bundle of fine fibres that leaves the olfactory peduncle, passes into the brain above the olfactory tubercle, joins the antero-ventral side of the anterior commissure and probably distributes impulses bilaterally to the nucleus of the stria terminalis and the central amygdaloid nucleus and also to the periventricular and granular layers of the contra-lateral olfactory bulb.

DISCUSSION

The olfactory areas in the human brain occupy a very similar position to those in the monkey's brain, although the relative increase in size of the neocortex and the entorhinal area in man has brought about some minor specific differences. Thus the frontal prepiriform area and the part of the anterior perforated substance receiving olfactory fibres in the human brain are both relatively smaller than they are in the brain of the monkey, and the olfactory parts of the cortico-medial group of amygdaloid nuclei (mainly the nucleus of the lateral olfactory tract and the medial amygdaloid nucleus) are in man even further reduced in size when compared with the prominent baso-lateral group than they are in the monkey.

The little evidence that is available from other sources fits in well with the location of the primary olfactory area in the gyrus ambiens, or, in other words, the anterior continuation of the hippocampal gyrus. In 1890, Jackson & Beevor described a tumour of the right temporo-sphenoidal lobe which had caused episodic disturbances in the form of olfactory seizures; the tumour was sharply circumscribed and the olfactory nerves were intact. Later the 'uncinate fits'—with olfactory hallucinations—came to be well known clinically: they are produced by irritative lesions which always directly or indirectly involve the region of the gyrus ambiens, and destruction of this part of the brain is followed by impairment of olfactory acuity (Frazier & Rowe, 1934).

The most satisfactory neuro-pathological material supports this conclusion also. Uyematsu (1921) has described two brains with unilateral destruction of the olfactory peduncle in which the resulting cellular atrophy is confined to the piriform area, 'lateral to the gyrus circumambiens and anterior to the uncus proper', and this area appears to correspond well to the temporal prepiriform cortex as delimited during the present investigation. Others (Tanaka, 1920; Stewart, 1939) have described degeneration in the cornu Ammonis and dentate fascia in arhinencephalic brains, but these findings are of little value because the cases were epileptics in which the hippocampal regions commonly show gliosis or other changes. Indeed, de Jongh (1927) describes a case with no trace of olfactory bulbs and tracts, and when the cornu Ammonis and dentate fascia were examined histologically they were found to be actually better developed than normal. It is thus unlikely that the hippocampal formation receives olfactory fibres directly, or even indirectly. Electrical stimulation of the hippocampus in conscious human patients does not give rise to any olfactory sensations (Penfield & Erickson, 1941). Moreover, in cases of epilepsy—in which the hippocampus often exhibits pathological changes—there does not appear to be any abnormality in the sense of smell.

SUMMARY

The secondary olfactory areas have been delimited in sections through three normal human brains. The olfactory tract fibres appear to end in the antero-lateral part of the olfactory tubercle, the dorsal and external parts of the anterior olfactory nucleus, the frontal and temporal parts of the prepiriform area, the cortico-medial group of amygdaloid nuclei and the nucleus of the stria terminalis. The positions of these areas on the surface of the brain and in representative frontal sections are shown in Pls. 1 and 2. Confirmatory evidence for some of the above conclusions is provided by the localization of the trans-synaptic atrophy in the cells of the prepiriform cortex resulting from accidental transection of the olfactory peduncle.

REFERENCES

ALLISON, A. C. (1953a). The morphology of the olfactory system in the vertebrates. *Biol. Rev.* **28,** 195–244.

ALLISON, A. C. (1953b). The structure of the olfactory bulb and its relationship to the olfactory tracts in the rabbit and the rat. *J. comp. Neurol.* **98,** 309–354.

BECK, E. (1934). Die Myeloarchitektonik der dorsalen Schläfenlappenrinde beim Menschen. *J. Psychol. Neurol., Lpz.,* **41,** 129–264.

BRODMANN, K. (1909). *Vergleichende Lokalizationslehre der Grosshirnrinde.* Leipzig: Barth.

CAJAL, S. R. (1911). *Histologie du Système Nerveux de l'homme et les vertèbres,* 2. Paris. Maloine.

CAMPBELL, A. W. (1905). *Histological Studies on the Localization of Cerebral Function.* Cambridge University Press.

CROSBY, E. C. & HUMPHREY, T. (1941). Studies of the vertebrate telencephalon. II. The nuclear pattern of the anterior olfactory nucleus, tuberculum olfactorium and the amygdaloid complex in adult man. *J. comp. Neurol.* **74,** 309–352.

DE JONGH, H. (1927). Ueber Arhinencephalie mit Hypertrophien im Gehirn. *Z. ges. Neurol. Psychiat.* **108,** 734–770.

ECONOMO, C. V. (1927). *Cytoarchitectonics of the Human Cerebral Cortex.* Oxford University Press.

FRAZIER, C. A. & ROWE, S. N. (1934). Certain observations upon localization in fifty-one verified tumours of the temporal lobe. *Res. Publ. Ass. nerv. ment. Dis.* **13,** 251–258.

HILPERT, P. (1928). Der Mandelkern des Menschen. I. Cytoarchitektonik und Faserverbindungen. *J. Psychol. Neurol.* **36,** 44–74.

JACKSON, J. H. & BEEVOR, C. E. (1890). Case of tumour of the right temporo-sphenoidal lobe bearing on the localization of the sense of smell and on the interpretation of a particular variety of epilepsy. *Brain*, 12, 346–357.

JOHNSTON, J. B. (1923). Further contributions to the study of the evolution of the forebrain. *J. comp. Neurol.* 35, 337–481.

MEYER, M. & ALLISON, A. C. (1949). An experimental investigation of the connexions of the olfactory tracts in the monkey. *J. Neurol. Psychiat.* 12, 274–286.

PENFIELD, W. and ERICKSON, T. C. (1941). *Epilepsy and Cerebral Localization. A Study of the Mechanism, Treatment and Prevention of Epileptic Seizures.* London.

ROSE, M. (1927a). Der Allocortex bei Tier und Mensch. *J. Psychol. Neurol.* 34, 1–112.

ROSE, M. (1927b). Die sog. Riechrinde beim Menschen und beim Affen. *J. Psychol. Neurol.* 34, 261–401.

ROSE, M. (1928). Die Inselrinde des Menschen und der Tiere. *J. Psychol. Neurol.* 37, 467–624.

ROSE, M. (1935). Cytoarchitektonik und Myeloarchitektonik der Grosshirnrinde. In Bumke and Foerster's *Handbuch der Neurologie*, 4, 32–37. Berlin.

STEWART, R. M. (1939). Arhinencephaly. *J. Neurol. Psychiat.* 2, 303–312.

TANAKA, F. (1920). Absence of lobus olfactorius and sclerosis of cornu Ammonis. *Arch. Neurol. Psychiat., Chicago*, 4, 151–170.

UYEMATSU, S. (1921). A study of the cortical olfactory apparatus. *Arch. Neurol. Psychiat., Chicago*, 6, 146–156.

VOGT, C. & VOGT, O. (1919). Allgemeinere Ergebnisse unsere Hirnforschung. Zweite Mitteilung: Das Weser der topischen architektonischen Differenzen des Cortex cerebri. *J. f. Psychol. u. Neur.* 25, 292–360.

WINKLER, C. A. (1918). The olfactory tract in the rabbit. In *Opera omnia*, 5, 397–413. Haarlem: F. Bohn.

LIST OF ABBREVIATIONS

|			
a.entorh.	entorhinal area	*n.amyg.cort.*	cortical amygdaloid nucleus
amyg.	amygdala	*n.amyg.lat.*	lateral amygdaloid nucleus
a.prepir.fr.	frontal part of the prepiriform area	*n.amyg.med.*	medial amygdaloid nucleus
		n.diag.b.	nucleus of the diagonal band
com.ant.	anterior commissure	*n.str.term.*	nucleus of the stria terminalis
com.ant.l.ant.	anterior limb of the anterior commissure	*pall.*	pallidum
		put.	putamen
gyr.hipp.	gyrus hippocampi	*sulcus.rh.*	sulcus rhinalis
gyr.rect.	gyrus rectus	*sulcus.semi-ann.*	sulcus semi-annularis
hipp.	hippocampus	*tr.olf.*	olfactory tract
n.amyg.bas.	basal amygdaloid nucleus	*tub.olf.*	olfactory tubercle
n.amyg.cent.	central amygdaloid nucleus		

EXPLANATION OF PLATES

### PLATE 1

Fig. 1. Dorsal aspect of the temporal lobe of the human brain (which has been cut away from the frontal lobe), × 2, showing the olfactory areas in the region of the uncus. The areas in which olfactory tract fibres probably terminate are indicated by dots.

Fig. 2. Orbital aspect of the frontal lobe of the human brain (which has been cut away from the temporal lobe), × 1·5, showing the position of the basal olfactory areas and the distribution of olfactory tract terminals (dotted).

Figs. 3 and 4. Representative frontal sections through the olfactory areas of the basal telencephalon of man. Cresyl violet stain, × 7·5. The olfactory tract is cross-hatched and the probable situation of olfactory tract terminals is indicated by dots.

PLATE 2

Figs. 5–8. Frontal sections through the basal telencephalic areas of the human brain. Cresyl violet stain, × 7·5. The olfactory tract is cross-hatched and the areas in which the olfactory tract fibres probably terminate are indicated by dots.
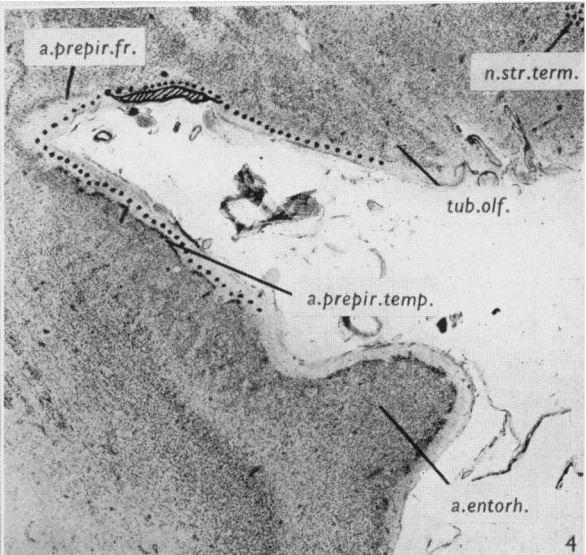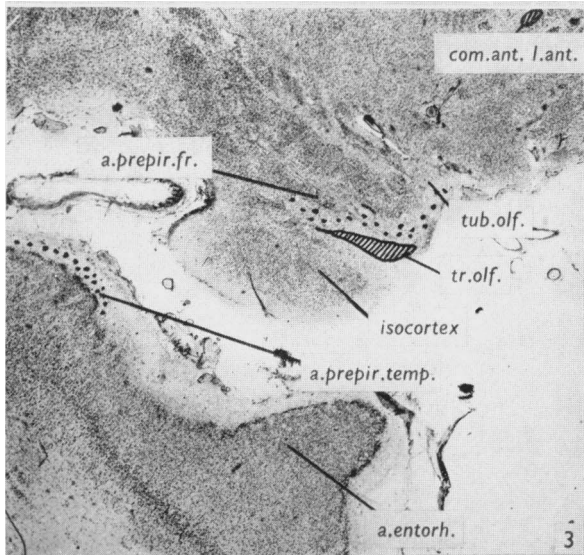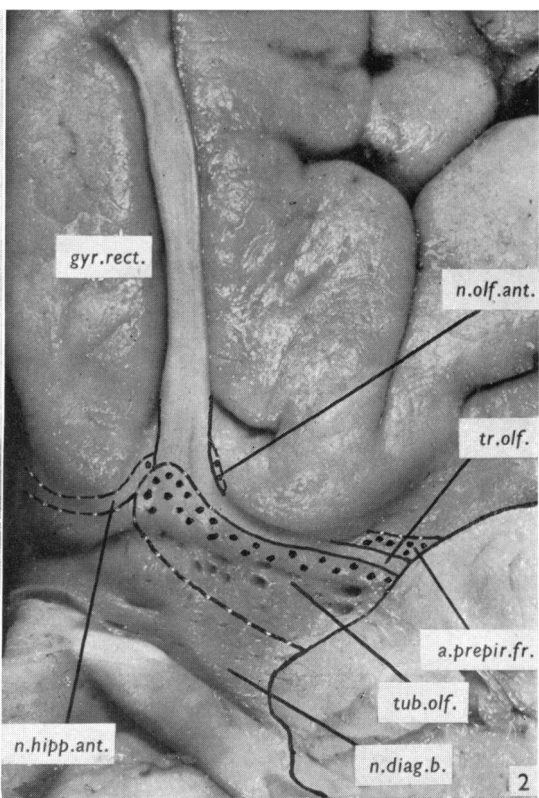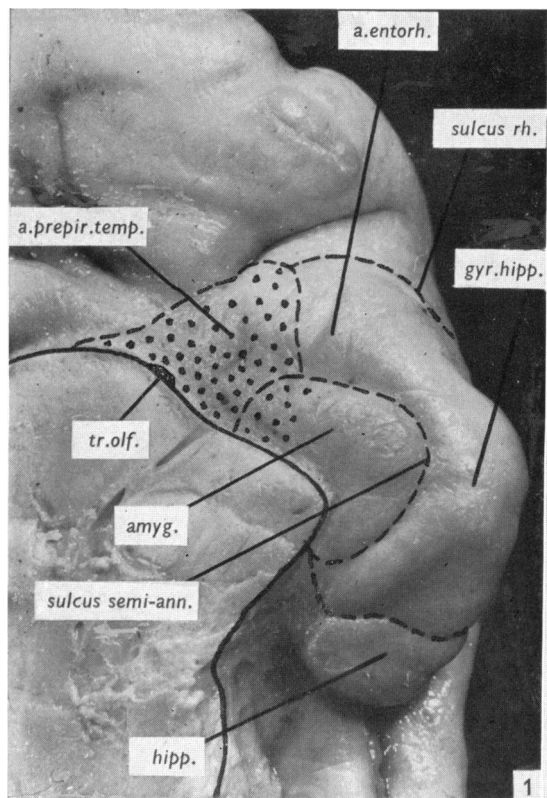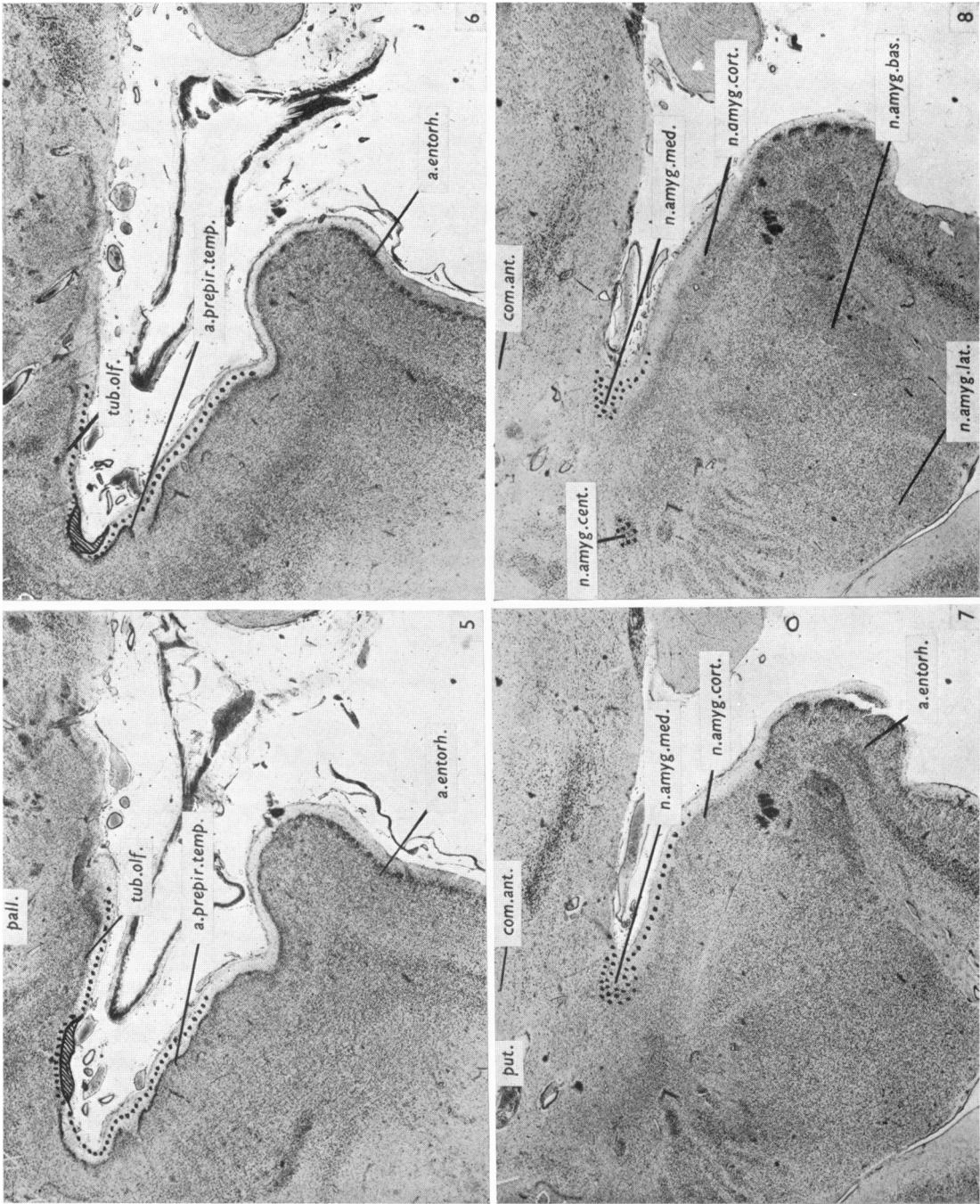
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